

We Claim:

1. A process for the preparation of S (-) 3-aryl-2-alkoxy propanoic acid derivatives of the formula (1a), wherein R¹ represents H or (C₁-C₆) alkyl group; R² represents (C₁-C₆) alkyl groups; R³ represents H, protecting groups such as benzyl, substituted benzyl, or (C₁-C₃) alkyl group, comprising steps of:

5 alkyl group, comprising steps of:

- (i) Selective O-alkylation or O-aralkylation of L-tyrosine of formula (2a) by

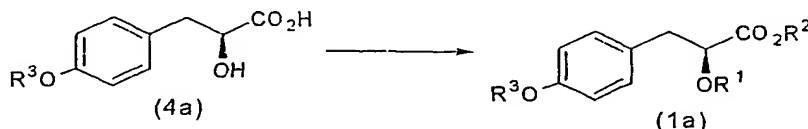
 - Reacting a base and a suitable chelating agent to obtain the copper complex,
 - Reacting the copper complex with an alkylating or aralkylating agent in the presence of suitable solvents and a base to obtain the compound of formula (3a), where R³ represents the corresponding alkyl or aralkyl group;



- (ii) Diazotisation of the compound of the formula (3a) using a diazotising agent, in suitable solvents in acidic media to obtain the compound of formula (4a)

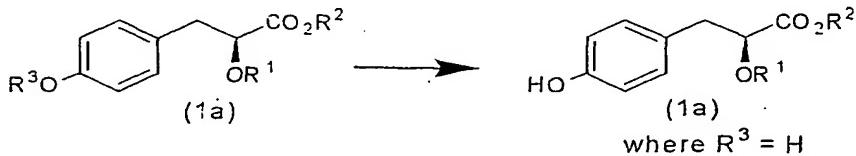


- 15 (iii) Dialkylation of the compound of formula (4a) using an excess of alkylating agent and excess base, in presence of suitable solvent to obtain optically and chemically pure compound of formula (1a), without resolution.



- (iv) Optionally, removing the excess alkylating agent

20 (v) Deprotection of the protecting group of compound of formula (1a) to obtain further compound of formula (1a), where $R^3 = H$, without resolution.

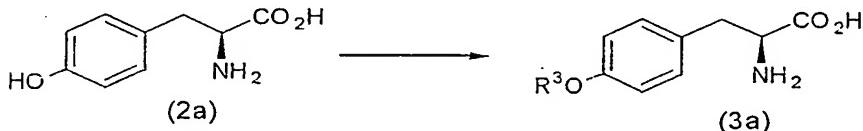


2. A process as claimed in claim 1 wherein the said base used in step (i) is selected from NaOH, KOH, K₂CO₃.

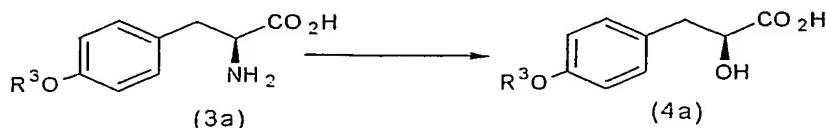
25 3. A process as claimed in claim 1 wherein the said chelating agent used in step (i) is selected from CuSO₄, Cu(OAc)₂.

4. A process as claimed in claim 1 wherein the said alkylating agent used in step (i) is selected from suitable (C_1 - C_3)alkyl halides and suitable aralkylating agent is selected from suitable benzyl or substituted benzyl halides.
5. A process as claimed in claim 1 wherein the said solvent used in step (i) is selected from methanol, ethanol, DMF or mixture thereof.
6. A process as claimed in claim 1 wherein the said diazotising agent used in step (ii) is sodium nitrite in presence of reagents selected from sulfuric acid, orthophosphoric acid, potassium hydrogen sulfate.
10. A process as claimed in claim 1 wherein the said solvent used in step (ii) is selected from dioxane, acetone, methyl ethyl ketone or mixture thereof.
15. A process as claimed in claim 1 wherein the said alkylating agent used in step (iii) is selected from suitable alkyl sulfates, alkyl halides, the base is selected from NaH, KOH, t-BuOK and the solvent used is DMSO.
9. A process for the preparation of S (-) 3-aryl-2-hydroxy propanoic acid derivatives of the formula (1a), wherein R^1 , R^2 & R^3 are as described in claim 1, comprising steps of :

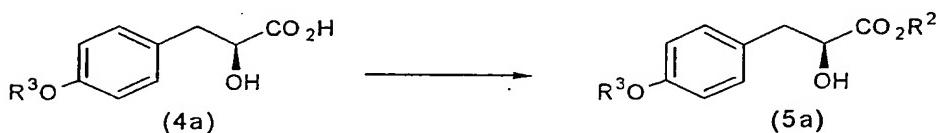
- (i) Selective O-alkylation or O-aralkylation of L-tyrosine of formula (2a) by
- a) Reacting a base and a suitable chelating agent to obtain the copper complex,
 - b) Reacting the copper complex with an alkylating or aralkylating agent in the presence of suitable solvents and a base to obtain the compound of formula (3a), where R^3 represents the corresponding alkyl or aralkyl group;



- (ii) Diazotisation of the compound of the formula (3a) using a diazotising agent, in suitable solvents in acidic media to obtain the compound of formula (4a)



- (iii) Selective esterification of compound of formula (4a) to obtain compound of formula (5a)

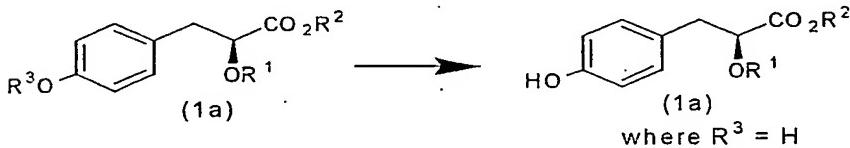


- (iv) O-alkylation of compound of formula (5a) using suitable alkylating agents in the presence of suitable bases to obtain compound of formula (1a),



- (v) optionally, removing the excess alkylating agent

- 5 (vi) Deprotection of the protecting group of compound of formula (1a) to obtain further compound of formula (1a), where R³ = H, without resolution.



10 10. A process as claimed in claim 9 wherein the said base used in step (i) is selected from NaOH, KOH, K₂CO₃.

11. A process as claimed in claim 9 wherein the said chelating agent used in step (i) is selected from CuSO₄, Cu(OAc)₂.

15 12. A process claimed in claim 9 wherein the said alkylating agent used in step (i) is selected from suitable (C₁-C₃)alkyl halides and suitable aralkylating agent is selected from suitable benzyl or substituted benzyl halides.

13. A process as claimed in claim 9 wherein the said solvent used in step (i) is selected from methanol, ethanol, DMF or mixture thereof.

20 14. A process as claimed in claim 9 wherein the said diazotising agent used in step (ii) is sodium nitrite in presence of reagents selected from sulfuric acid, orthophosphoric acid, potassium hydrogen sulfate.

15. A process as claimed in claim 9 wherein the said solvent used in step (ii) is selected from dioxane, acetone, methyl ethyl ketone or mixture thereof.

25 16. A process as claimed in claim 9 wherein selective esterification of (4a) to obtain compound of formula (5a), in step (iii), is carried out using corresponding alcohols such as MeOH, EtOH, propanol, isopropanol, butanol, isobutanol, tert-butanol in the presence of reagents selected from H₂SO₄, SOCl₂, p-TSA or mixtures thereof.

30 17. An alternate process for the selective esterification of (4a) to obtain compound of formula (5a), as claimed in claim 9, in basic conditions using suitable bases selected from Na₂CO₃, K₂CO₃, KOH, NaOMe, NaOEt or mixtures thereof in the presence of

corresponding alkylating agents such as methyl iodide, ethyl iodide, dimethyl sulfate, diethyl sulfate in solvents selected from DMF, DMSO or mixtures thereof.

18. A process as claimed in claim 9, wherein the O-alkylation of compound of formula (5a) in step (iv) is carried out using suitable alkylating agents selected from alkyl sulfates such as diethyl sulfate, dimethyl sulfate; alkyl halides selected from methyl iodide, ethyl iodide, ethyl bromide, propyl bromide and isopropyl bromide. The solvent used is DMSO.

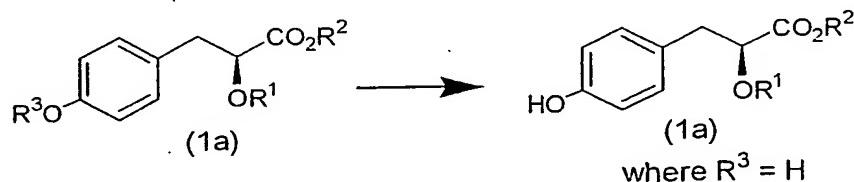
19. A process as claimed in claim 9, step (iv) wherein suitable bases are NaH, KOH, t-BuOK.

10 20. A process as claimed in claims 1 and 9 wherein the deprotection of compound of formula (1a) where R³ = protective group, to obtain further compounds of formula (1a), where R³ = H, is carried by treating with suitable Lewis acids selected from AlCl₃, BF₃ etherate, BF₃ acetate and suitable nucleophiles selected from suitable alkylthiols such as ethanethiol, propanethiol, ethanedithiol, alkyl aryl sulfides and dialkyl sulfides, preferably aryl alkyl sulfides, more preferably thioanisole.

15 21. A process as claimed in claims 1 and 9 wherein the deprotection of compound of formula (1a), where R³ = protective group, to obtain further compounds of formula (1a), where R³ = H, is alternatively carried by catalytic transfer hydrogenation using metal catalysts such as Pd/C at atmospheric pressure in the presence of a hydrogen donor reagent, in a suitable solvent selected from ethyl acetate, THF, dioxane, glacial acetic acid, methanol, ethanol, propanol, isopropanol or mixtures thereof.

20 22. A process as claimed in claim 21 wherein suitable hydrogen donor reagent is selected from ammonium formate, cyclohexene, 1,4-cyclohexadiene.

25 23. A process for the preparation of compound of formula (1a), where R³ = H, with chiral purity ≥ 99%, by deprotecting compound of formula (1a), when R³ represents a protective group as defined earlier, by treating with suitable Lewis acids selected from AlCl₃, BF₃ etherate, BF₃ acetate and suitable nucleophiles selected from ethanethiol, propanethiol, ethanedithiol, alkyl aryl sulfides and dialkyl sulfides.



30 24. A process as claimed in claims 1 & 9 wherein the excess alkyl halide is removed by vacuum distillation or reacting with trialkyl amines preferably triethyl amine.

25. A process as claimed in claims 1 & 9 wherein the excess alkyl sulfate is removed by treating with organic base such as trialkylamines preferably, triethylamine and diisopropyl ethylamine.

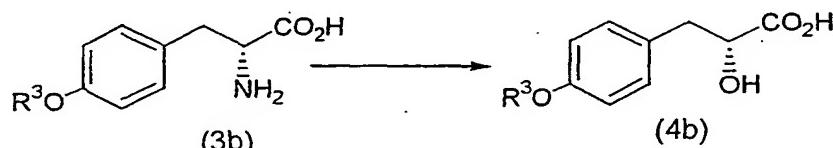
26. A process for the preparation of R (+) 3-aryl-2-alkoxy propanoic acid derivatives of the formula (1b), wherein R¹ represent H or (C₁-C₆) alkyl; R² represents (C₁-C₆) alkyl group; R³ represents H, protecting groups such as benzyl, substituted benzyl, or (C₁-C₃) alkyl group, comprising:

- (i) Selective O-alkylation or O-arylation of D-tyrosine of formula (2b) by

 - Reacting a base and a suitable chelating agent to obtain the copper complex,
 - Reacting the copper complex with an alkylating or aralkylating agent in the presence of suitable solvents and base to obtain the compound of formula (3b), where R³ represents corresponding alkyl or aralkyl group;



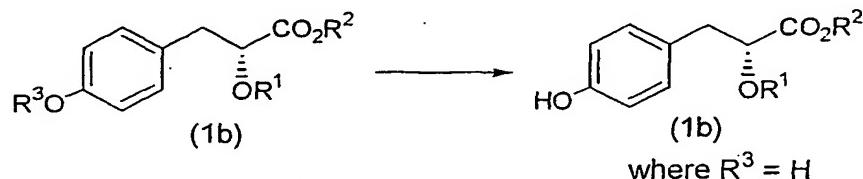
- (ii) Diazotisation of the compound of the formula (3b) using a diazotising agent, in suitable solvents in acidic media to obtain the compound of formula (4b)



- (iii) Dialkylation of the compound of formula (4b) using an excess of alkylating agent and excess base, in presence of suitable solvent to obtain optically and chemically pure compound of formula (1b), without resolution.

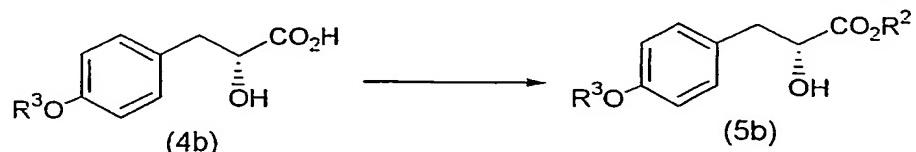


- (iv) Optionally, removing the excess alkylating agent
 - (v) Deprotection of the protecting group of compound of formula (1b) to obtain further compound of formula (1b), where R³ = H, without resolution.

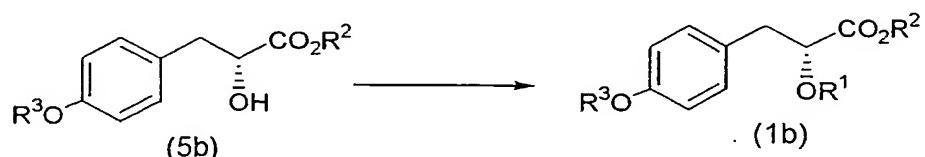


27. A process for the preparation of R (+) 3-aryl-2-alkoxy propanoic acid derivatives of the formula (1b), where all symbols are as defined earlier, the process comprising

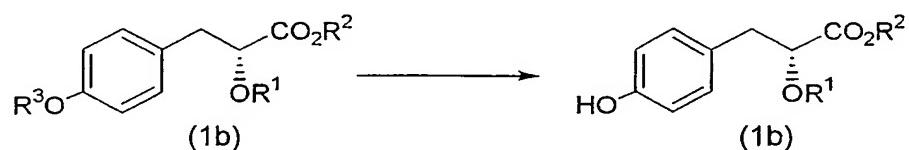
- (i) converting the compound of formula (4b) to compound of formula (5b),



- (ii) subsequently, converting the compound of formula (5b) to compound of formula (1b),



- (iii) optionally, converting the compound of formula (1b), to further compounds of formula (1b), where $R^3 = H$, without resolution



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